Milestones and Monitoring in Patients with CML Treated with Imatinib

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Imatinib is the therapeutic standard for newly diagnosed patients with chronic myeloid leukemia (CML). Recent updates of the IRIS trial, a study of standard-dose imatinib in newly diagnosed chronic-phase patients treated with 400 mg imatinib daily, suggest a stabilization of progression-free survival curves at a high level, implying that the majority of patients will do well on standard therapy. However, some 20% to 30% of patients will fail on imatinib and require alternative therapies. Identification of those patients likely to fail would be desirable to allow for more intensive therapy up front. After a brief overview of the history of CML, this paper will review current recommendations for staging of CML patients at diagnosis. Next, the various tests used to monitor their response to imatinib will be discussed in the context of the currently accepted criteria for imatinib failure and suboptimal response. Last, approaches to identify high-risk patients at diagnosis will be addressed.

Chronic Myeloid Leukemia: A Long Story with a Happy End?

Chronic myeloid leukemia (CML) has left more marks in the history of medicine than many other much more common diseases. Its narrative goes back to 1845, when John Hughes Bennett, an Edinburgh pathologist, described a "Case of Hypertrophy of the Spleen and Liver in which Death Took Place from Suppuration of the Blood." Only a few weeks later, Rudolf Virchow in Berlin published a very similar case. Although we cannot know for sure, it is likely that these two patients indeed suffered from CML. While Bennett thought that the disease represented an infection, Virchow recognized its cancerous nature and soon after coined the term "leukemia." The dispute over which one of them had identified it first and whether the disease was an infection or a cancer was eventually settled cordially, with Virchow acknowledging Bennett's priority and Bennett recognizing the neoplastic nature of leukemia. Ironically, both were actually preceded by Alfred Donné of Paris, who described what was obviously leukemia a year earlier but did not provide enough detail. The next big step came in 1872, when Ernst Neumann recognized that leukemia originated in the bone marrow. It then took almost 100 years for the next quantum leap, the discovery by Peter Nowel and David Hungerford of an abnormally small G-group chromosome, the first consistent karyotypic abnormality associated with cancer. Thirteen years later, Janet Rowley recognized that the minute chromosome, now dubbed "Philadelphia chromosome" (Ph), was in fact the product of a reciprocal translocation between chromosomes 9 and 22. The following 25 years saw the identification of the translocation partners as BCR and ABL, the discovery that unregulated tyrosine kinase activity is critical to BCR-ABL's ability to transform cells to malignancy and the establishment of a murine disease model. Therapy developed slowly. Arsenicals had been in use for cancer treatment since ancient times, and in 1865 Heinrich Lissauer, better known for his contributions to neurology, reported the use of arsenic in two patients with leukemia. As a curiosity, Conan Doyle, the author of the Sherlock Holmes detective stories, reported in 1882 in *The Lancet* on a patient with the clinical presentation of CML who achieved a partial response to arsenicals. Soon after the discovery of the X-ray, splenic irradiation was introduced for symptomatic relief and remained the mainstay of therapy for the first half of the 20th century. The first drug used with consistent activity was busulfan, introduced in 1959. Some 10 years later, hydroxyurea became available, which is probably the first intervention that significantly prolonged survival in CML. A breakthrough was achieved in the mid-1970s when the Seattle group reported the disappearance of the Ph-positive cell clone in CML patients treated with allogeneic stem cell transplants, the first cures of CML that we know of. The early 1980s saw the introduction of interferon-α as the standard drug therapy. In contrast to all other drugs known at the time, interferon-α led to complete cytogenetic responses and long-term survival, although only in a subset of patients. In 1992, Alexander Levitzki suggested that inhibiting ABL with small molecules called tyrphostins might be useful to treat leukemias driven by ABL oncogenes. At about the same time, Alois Matter, Jürg Zimmermann, and Nick Lydon at Ciba-Geigy had synthesized a compound termed GCP57148B (now known as imatinib) that inhibited ABL and several other tyrosine kinases at submicromolar concentrations. Clinical trials initiated by Brian Druker, much against the skepticism of the manufacturer, rapidly established the compound's activity in patients with CML and revolutionized CML

therapy. Now, in 2008, the majority of patients diagnosed with chronic-phase CML can expect to have long-term remissions with good quality of life. For the 20% to 30% who fail therapy, second-line inhibitors are a good therapeutic option. However, once the disease has progressed beyond the chronic phase, allogeneic stem cell transplant is still the recommendation for all eligible patients. Even more importantly, it seems that therapies directed at the BCR-ABL tyrosine kinase are not curative since they fail to eradicate the CML stem cells. Thus, the CML saga is not yet finished, and much work remains to be done.

Current CML Therapy

Current recommendations for the initial therapy of newly diagnosed patients with chronic-phase CML are based on the results of the pivotal IRIS (International Randomized Study of Interferon and STI571) trial. The 72-month update of this study showed an estimated overall survival of 88% for patients treated up front with 400 mg imatinib daily (referred to as standard-dose imatinib). All in all, 66% of patients were still on study receiving imatinib, 14% had progressed, and 5% had discontinued imatinib because of side effects.[1] The remaining patients had left the study for a variety of other reasons, such as withdrawal of consent or protocol violations. Importantly, the rate of therapeutic failure peaked in year 2 with a steady decline thereafter, suggesting that a subset of patients is destined to fail while the remaining cohort is stabilizing at a high level. Consistent with this finding, patients who achieved a complete cytogenetic response (CCyR) and maintained it for 4 years had a zero risk of progression to accelerated phase or blast crisis. In a recent single-center report of similar patients, there was a 25% rate of discontinuation at 5 years, mainly for lack of efficacy. An additional 9% of patients had failed to achieve a major cytogenetic response (MCyR), while maintaining their complete hematologic response (CHR).[2] A realistic expectation is, therefore, that while the majority of patients will do well with the therapeutic standard, some 20% to 30% of newly diagnosed patients will require alternative treatments. These are the patients at whom efforts to improve outcomes must be directed. Currently, the main tool to identify high-risk patients is close monitoring of their in vivo response to therapy, using the reduction of leukemia load at a given time to define milestones that predict the future progression risk.

Ordering the Right Test at the Right Time

Collecting a complete set of baseline data is mandatory (**Table 1**) and requires a clinical exam with documentation of spleen size (in cm below the left costal margin), complete blood count (CBC) with white blood cell differential, and bone marrow biopsy with metaphase karyotyping. Without these parameters, neither the disease phase nor the Sokal risk score (for patients with chronic phase) can be determined, both of which measurements may impact the choice of therapy. Fluorescence in situ hybridization (FISH) or *qualitative* (low sensitivity) PCR for BCR-ABL are necessary to exclude a cryptic BCR-ABL rearrangement if a myeloproliferative disease (MPD) is suspected, but cytogenetics is Ph-negative or technically unsatisfactory. However, as a rule, FISH should not replace metaphase karyotyping, since additional clonal chromosomal abnormalities in the Ph-positive cells (clonal cytogenetic evolution, or CCE) would be missed. While the prognostic significance of CCE in newly diagnosed patients has not yet been clarified, CCE developing on therapy indicates a high risk of relapse, and baseline information is needed for comparison. At this point it may be wise to consider the presence of CCE at diagnosis as a warning sign, similar to a high Sokal risk score. FISH has been advocated for the detection of

Table 1. Indications for diagnostic tests.

Test	Indication
Physical exam	Diagnosis/staging Every 3-month until resolution of splenomegaly Suspected progression or resistance
Complete blood count	Diagnosis/staging Every 1-2 weeks until blood counts have stabilized, then at 6 weeks intervals Suspected progression or resistance
Bone marrow metaphase karyotyping	Diagnosis/staging 6, 12, 18 months or until complete cytogenetic response Suspected progression or resistance
Quantitative PCR for BCR-ABL	Every 3 months once CCyR documented
FISH for BCR-ABL (peripheral blood)	Uncertain diagnosis (typical clinical presentation, but metaphase cytogenetics not successful or Philadelphia-chromosome negative) Every 3 months if no access to high quality quantitative PCR monitoring
Qualitative (low sensitivity) PCR for BCR-ABL	Uncertain diagnosis (typical clinical presentation, but metaphase cytogenetics not successful or Philadelphia-chromosome negative)
BCR-ABL kinase mutation screen	Suspected progression or resistance

deletions flanking the BCR-ABL breakpoint, since initial studies suggested these deletions may adversely affect the durability of responses to imatinib, at least in patients with late chronic phase.[3] As studies in newly diagnosed patients have not confirmed this initial finding, FISH is not mandatory if the presence of BCR-ABL is demonstrated by conventional karyotyping.[4,5] Confusion can result when highly sensitive PCR tests are applied to diagnostic samples. Low-level BCR-ABL positivity detected in this situation may reflect small BCR-ABL–expressing subclones in an otherwise Ph-negative MPD, similar to the occurrence of BCR-ABL transcripts in some healthy individuals.[6] While the overall significance of such clones in the context of MPD is unknown, they do not indicate that this particular disease is sensitive to imatinib and should not impact therapeutic decisions. Of note, a baseline *quantitative* PCR (qPCR) at diagnosis is neither required as a comparison for subsequent follow-up, nor has the pre-therapeutic BCR-ABL level prognostic significance.[7]

Monitoring on Treatment

Blood counts and bone marrow karyotyping

Complete blood counts should be performed at least weekly until they have stabilized, with greater intervals thereafter. Once CHR has been documented, monitoring continues with karyotyping of at least 20 bone marrow metaphases, which is currently recommended at 6, 12, and 18 months, or until CCyR has been achieved. Reasons why conventional cytogenetic analysis has maintained its role for response monitoring include its high level of standardization, wide availability, the fact that much of the prognostic information from the IRIS trial is based on cytogenetics, and the ability to detect CCE. There is debate whether patients with a documented CCyR should continue to have annual or biannual bone marrow karyotyping in the absence of a rise in BCR-ABL transcript levels. Those in favor have argued that some 5% to 10% of patients with a CCyR develop clonal cytogenetic abnormalities in their Ph-negative cells (CCA/Ph$^-$), sometimes with progression to a myelodysplastic syndrome (MDS) or even to acute myeloid leukemia (AML).[8,9] However, in the largest published series, the outcome of patients with MCyR was not influenced by the presence of CCA/Ph$^-$.[10] The exception to this rule may be patients with monosomy 7, where an accumulation of case reports suggests a high risk of MDS/AML. Since these individuals identify themselves by low blood counts, outside of a clinical trial our approach is to limit marrow karyotyping to CCyR patients with a rise of BCR-ABL transcripts or with persistent or newly acquired cytopenias.

Fluorescence in situ hybridization

FISH for BCR-ABL on peripheral blood is not infrequently used to follow patients on therapy. Advocates cite the good correlation with marrow cytogenetics that was shown in a retrospective study.[11] Nevertheless, one should realize that correlation is not equivalent to concordance and that other studies came to less favorable results, implying that FISH and cytogenetics results may differ significantly in individual patients.[12,13] Another argument against the use of FISH for routine monitoring is that it has never been validated in a clinical trial with real endpoints. Additionally, some commercial labs continue to use old-fashioned probes with a high false-positive rate or fail to indicate their lab-specific cutoffs, both of which render the interpretation of the results impossible. At this point, the recommendation is to use FISH only if there is no access to high quality qPCR monitoring.

Quantitative RT-PCR for BCR-ABL

Once CCyR has been documented, qPCR should be performed at three-month intervals.[14] Exploiting the full potential of this technology in a routine clinical setting can be challenging for a number of reasons. While qPCR testing for BCR-ABL is offered by many academic and commercial labs, the assays are not yet fully standardized, and their quality is variable. A frequent deficiency is the lack of an indication of the test sensitivity for a given sample, a measure that is dependent on the quantity and quality of the specimen. For example, degradation due to a long transit time can dramatically reduce sensitivity, leading to false-negative results.[14] Another problem is that results are not yet uniformly expressed and thus not comparable between different labs. Much effort has been made to improve the standardization of qPCR for BCR-ABL, including the choice of suitable control genes and a uniform way of expressing the results.[14] Provided that certain quality requirements are fulfilled, individual laboratories will be able to continue using their established technology, employing a laboratory-specific conversion factor to express their data on an "international scale."[14] A value of 100% on this scale approximates the average BCR-ABL level of the newly diagnosed patients used to establish the baseline for the IRIS study. A value of 0.1% corresponds to a 3-log reduction of BCR-ABL levels and is referred to as a major molecular response (MMR). MMR after 12 months of therapy is associated with a very low risk of relapse.[15] The definition of a complete molecular response (CMR), i.e., the absence of *detectable* transcripts, is still somewhat controversial. However, there appears to be an emerging consensus that CMR should be based on confirmed negativity by "nested PCR," which in most labs is more sensitive than qPCR by approximately one order of magnitude.[14] Importantly, confirmation in an independent sample drawn several weeks after the first is required. CMR predicts a very low risk of relapse, but it is not equivalent to disease eradication.[16]

Screening for kinase domain mutations

Mutations in the kinase domain of BCR-ABL are a frequent mechanism of resistance to imatinib, and may instruct clinical decisions (discussed below). However, current evidence does not support mutation screening on a routine basis unless there is an indication for a loss of response. In fact, transient detection of kinase domain mutations has been documented in some patients with stable CCyR, suggesting that the detection of a mutation in the absence of an increase in leukemia burden is uninterpretable.[17]

Imatinib plasma levels

A recent study found that the imatinib trough levels were higher in patients with a CCyR or MMR compared with patients with a less profound response.[18] In the IRIS trial, patients with low day-29 imatinib trough concentrations were less likely to achieve a CCyR and MMR, suggesting that measuring plasma concentrations may identify patients who would benefit from a dose escalation.[19] Given that no interventional data are available, plasma level monitoring is not currently part of routine management. However, measuring plasma concentrations may be useful in the case of resistance or unusually severe side effects.[20]

Diagnosing Imatinib Resistance

Primary imatinib resistance

Primary imatinib resistance is a time-dependent diagnosis that is defined as the failure to achieve a certain level of response at a given time after initiating therapy. Secondary resistance is defined as a confirmed increase of leukemia load at any time during therapy. An expert panel convened by the European LeukemiaNet (ELN) has made recommendations for therapeutic milestones that have been widely accepted and are included in the National Comprehensive Cancer Network guidelines.[21,22] The ELN recommendations classify responses as optimal, suboptimal, and failure. An optimal response implies that the patient is likely to do well on imatinib. In case of a suboptimal response, continuation of imatinib is acceptable, but adjustments are likely to become necessary in the future. Failure implies that a change of therapeutic strategy is required (**Figure 1**; see Color Figures, page 497).

The first therapeutic milestone is based on the evaluation after 3 months of therapy. At this time, a CHR defines an optimal response. Of note, according to the ELN recommendations, a partial hematologic response (PHR) is considered a suboptimal response. In practice, however, applying this definition has proven difficult since PHR encompasses a very wide range of responses, from persistence of minimal palpable splenomegaly to significant leukocytosis—two scenarios with very different prognostic implications. It is therefore anticipated that the definition of a suboptimal response at 3 months will be revised in an updated version of the recommendations. No cytogenetic response is mandated at three months, thus no bone marrow biopsy with cytogenetics is recommended. At 6 months, an optimal response warrants MCyR (< 36% Ph-positive metaphases); a suboptimal response warrants at least a minor or minimal cytogenetic response (36% to 95% Ph-positive metaphases); and no cytogenetic response implies failure. At 12 months, a CCyR equals an optimal and a PCyR a suboptimal response. At 18 months, optimal response is defined as a MMR, while CCyR is equal to a suboptimal response.

The data used to justify these recommendations are based on the IRIS study and on a common sense judgment as to what constitutes an acceptable outcome. For example, a patient without any cytogenetic response at 3 months has a 55% (95%CI: 37-73%) chance of achieving CCyR by 42 months, while the likelihood is only 22% (95%CI: 0-44%) in a patient without a cytogenetic response at 6 months.[23] It is evident that the definition of what is acceptable is influenced by the efficacy and risks of alternative therapies as well as the patient's individual circumstances. Thus, with the availability of the second-line ABL inhibitors dasatinib and nilotinib as low-toxicity options, recommendations may change. Furthermore, there is considerable imprecision (e.g., large confidence intervals), which is due to the low rate of failure in the IRIS study. For example, the category of suboptimal response has been questioned by a recent report indicating that the outcome of patients who have this response at 3 and 6 months may be similar to the outcome of patients with failure.[24] Another important aspect is that the data apply to patients treated with standard-dose imatinib; one would expect that more stringent response criteria will apply to patients treated with higher doses of imatinib. An update of the recommendations is currently in preparation.

Secondary imatinib resistance

Secondary imatinib resistance implies the loss of response from any given level, such a CHR or MCyR. It is good practice to confirm subtle changes in the response level before making major alterations to therapy. What constitutes a significant rise of BCR-ABL transcripts in patients followed with qPCR has been a matter of debate. Cutoffs between two- and tenfold have been proposed, reflecting differences in assay performance.[14,25] In the absence of other indications of resistance, any transcript rise should be confirmed in a second sample, particularly if it occurs at low levels, where the imprecision of BCR-ABL quantification is greatest.

Resistance workup

Every resistance workup starts with a thorough history to ascertain the patient's adherence to the prescribed drug regimen. Financial pressures may also cause patients to cut down on their drug dose. Sadly, this "economic" imatinib

resistance is not limited to the developing world but is increasingly common in the faltering health care system of the United States. Measurement of imatinib plasma concentrations has been proposed to diagnose non-compliance. However, the pre-planning required for obtaining a sample that reflects trough concentrations largely defeats this purpose. No marker is available yet to measure cumulative imatinib exposure over time, in analogy to HbA1C in diabetics. Once a rise of BCR-ABL transcripts has been confirmed and compliance ascertained, physical exam, CBC, bone marrow morphology, karyotyping, and screening for BCR-ABL kinase domain mutations are indicated to direct salvage therapy. The most important piece of information is whether a patient's CML has progressed beyond chronic phase. If so, responses to second-line inhibitors are unlikely to last, and an allogeneic stem cell transplant should be offered to eligible patients, using nilotinib or dasatinib as a bridge.[26-28] Mutation analysis provides additional information. Patients with the broadly resistant T315I mutant will not benefit from any of the currently approved ABL inhibitors. Other mutations, while not conferring complete resistance, influence the depth of response.[27,29] For example, E255K/V is relatively resistant to nilotinib, while F317L/I is relatively resistant to dasatinib in vitro (**Figure 2**; see Color Figures, page 497). Consistent with this finding, CCyR is rare in E255K/V patients treated with nilotinib and in F317L/I patients treated with dasatinib. Although prospective intervention studies are not yet available, it seems prudent to utilize this information to choose between available kinase inhibitors. The diagnosis of imatinib resistance has significant prognostic implications and should not be taken lightly. It is likely that imatinib resistance reveals more about the biology of the disease than the classical, mostly morphology-based parameters used to define disease phase. Resistance mandates a careful reevaluation of the situation and all available therapeutic options.

Suboptimal Response and Warning Signs

A suboptimal response according to ELN recommendations implies that the long-term benefits of imatinib are doubtful. For example, a partial but not a CCyR at 12 months is classified as suboptimal. The therapeutic implications are less straightforward than for resistance, and good clinical judgment is needed. For example, a slow but continuous decrease of Ph-positive metaphases may be more favorable prognostically than an initial decrease followed by a plateau. Given that the durability of CCyR appears to be the same whether it was achieved early or late,[30] the challenge is to weigh the benefits of continuing imatinib as an agent with an excellent safety record in the hope of achieving the desired response versus the risk of potentially looming relapse. CCE and kinase domain mutants with a low level of resistance are warning signs of an increased risk for subsequent acquired resistance. Although not an immediate threat, these findings indicate that the leukemic clone is genetically unstable, and that it is more likely to become overtly resistant in the future.

Approaches to Predict Response Up-Front

The best clinical predictor of response is the Sokal score, which is based on peripheral blood blasts, platelets, spleen size, and age. At the 48-month update of the IRIS trial, patients with a high Sokal score had a 69% probability of achieving a CCyR compared with 84% and 91% for patients with an intermediate and low Sokal risk, respectively. The lower rate of CCyR is the basis for clinical trials of "high dose" imatinib (800 mg daily) in patients with a high Sokal risk that are currently in progress. In contrast to patients treated with interferon-α, the favorable prognostic impact of a CCyR on imatinib overcomes a high pre-therapeutic risk. Thus, efforts have been made to develop tools to identify those chronic phase CML patients who will fail to achieve a CCyR irrespective of their risk at diagnosis.

Gene expression profiling

Several studies applied expression array analysis to pre-therapeutic specimens and reported gene classifiers that predicted cytogenetic response.[31-33] Given that different starting materials (unselected white blood or bone marrow cells, mononuclear cells, or whole blood), array platforms, and bioinformatics tools were used, it is perhaps not surprising that there is no overlap between the gene lists associated with response. More important is that none of the studies used a sufficiently powered independent validation sample, and none of the classifiers has yet evolved into a clinical tool. Since practically all patients achieve CHR, one could also argue that the bulk of the leukemia cells are sensitive to imatinib, and predicting response will require analysis of progenitor or stem cells. In fact, we have been able to identify and validate a 75-gene predictor of cytogenetic response using $CD34^+$ cells.[34]

Drug transporters

There is a good correlation between intracellular imatinib concentrations and the phosphorylation of CRKL, a rather specific substrate of BCR-ABL that is commonly used as a surrogate of BCR-ABL kinase activity. Several drug transporters, including ABCB1 (PGP, the product of MDR1), hOCT1, and ABCG2 (BCRP) have been implicated in transmembrane shuttling. The most compelling data are available for hOCT1, an ATP-dependent outside-inside transporter of organic cathions. Patients with high expression of hOCT1 or activity (as determined by inhibition of hOCT1 activity with pharmacological blockers) are more likely to attain CCyR and MMR than patients with low hOCT1 activity.[35-37] This difference is particularly striking in patients treated with standard doses of imatinib, while higher doses

seem to at least partially overcome the adverse effect of low hOCT1 expression. These data suggest that measuring hOCT1 expression or activity may be useful for risk stratification. While a number of studies have demonstrated that imatinib is a substrate for ABCB1, there does not seem to be a clear association between ABCB1 expression and subsequent response to therapy. However, upregulation of ABCB1 expression may occur on treatment and promote relapse.[37] An important consideration is that expression levels alone may not tell the full story. In fact, polymorphisms of ABCG2, hOCT1 and CYP3A4 (the p450 enzyme primarily responsible for imatinib metabolism) have been implicated in imatinib response and resistance.[38, 39] As with gene array data, this preliminary observation awaits confirmation in an independent cohort.

Ex vivo sensitivity testing

An alternative approach to prognosticate response is ex vivo exposure of CML cells to imatinib to determine their individual sensitivity to drug. One study measured CRKL phosphorylation in extracts of leukemia cells exposed to imatinib in vitro and correlated the IC_{50} (the concentration at which pCRKL is reduced by 50%) with subsequent molecular response. Patients with a low IC_{50} had a higher likelihood of achieving MMR than patients with a high IC_{50}. However, this distinction was limited to patients with low Sokal risk, suggesting that insufficient BCR-ABL inhibition is unlikely to be the cause of failure in patients with high Sokal risk.[40] Another study used FACS to analyze total phosphotyrosine in $CD34^+$ cells exposed to imatinib and found a significant correlation between in vitro sensitivity and MCyR.[41] An alternative to measuring substrate phosphorylation as a correlate of BCR-ABL activity is to monitor events downstream of BCR-ABL kinase activity, such as WT1 mRNA expression.[42] Finally, in vitro drug sensitivity assessed by colony forming assays was shown to correlate with cytogenetic response in patients with late chronic phase but not myeloid blast crisis.[42,43] In vitro growth assays have the advantage of measuring composite endpoints that reflect a variety of biological features. However, they remain focused on the leukemia cells and do not take into account that the microenvironment may contribute to resistance. A candid assessment in mid-2008 comes to the conclusion that none of the approaches to predict response up-front has become part of clinical practice, because they are either too cumbersome or lack reproducibility. Thus, so far, the in vivo response continues to be the most valuable prognostic indicator.

Outlook

Imatinib has made CML therapy much more effective and seemingly much easier. However, a closer look reveals that exploiting the full potential of the available therapeutic options is a complex task that requires sophisticated knowledge of monitoring technologies and time-dependent response markers. What appears straightforward from the "ivory tower" perspective of academic centers poses a significant challenge to busy practitioners who treat a few CML patients along with a broad range of patients with other types of cancer. With the availability of effective and well-tolerated second-line agents, identifying those CML patients who fail standard therapy has become even more important. Test results and their over- and under-interpretation are a major source of error and confusion. In this labyrinth, the ELN recommendations provide orientation for when it is critical to sit down with the patient to assess whether a change of strategy is required. In case of doubt, it is appropriate to contact an academic center for advice or refer the patient for evaluation. Imatinib has changed the face of CML. Now the challenge is to exploit its full potential in all patients.

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